The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation

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Abstract: A core aspect of the human self is the attribution of personal relevance to everyday stimuli enabling us to experience our environment as meaningful [1]. However, abnormalities in the attribution of personal relevance to sensory experiences are also critical features of many psychiatric disorders [2, 3]. Despite their clinical relevance, the neurochemical and anatomical substrates enabling meaningful experiences are largely unknown. Therefore, we investigated the neuropharmacology of personal relevance processing in humans by combining fMRI and the administration of the mixed serotonin (5-HT) and dopamine receptor (R) agonist lysergic acid diethylamide (LSD), well known to alter the subjective meaning of percepts, with and without pretreatment with the 5-HT2AR antagonist ketanserin. General subjective LSD effects were fully blocked by ketanserin. In addition, ketanserin inhibited the LSD-induced attribution of personal relevance to previously meaningless stimuli and modulated the processing of meaningful stimuli in cortical midline structures. These findings point to the crucial role of the 5-HT2AR subtype and cortical midline regions in the generation and attribution of personal relevance. Our results thus increase our mechanistic understanding of personal relevance processing and reveal potential targets for the treatment of psychiatric illnesses characterized by alterations in personal relevance attribution.

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The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation

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Summary

A core aspect of the human self is the attribution of personal relevance to everyday stimuli enabling us to experience our environment as meaningful [1]. However, abnormalities in the attribution of personal relevance to sensory experiences are also critical features of many psychiatric disorders [2, 3]. Despite their clinical relevance, the neurochemical and anatomical substrates enabling meaningful experiences are largely unknown. Therefore, we investigated the neuropharmacology of personal relevance processing in humans by combining functional magnetic resonance imaging (fMRI) and the administration of the mixed serotonin (5-HT) and dopamine receptor (R) agonist lysergic acid diethylamide (LSD), well known to alter the subjective meaning of percepts, with and without pretreatment with the 5-HT_{2A}R antagonist ketanserin. General subjective LSD effects were fully blocked by ketanserin. In addition, ketanserin inhibited the LSD-induced attribution of personal relevance to previously meaningless stimuli and modulated the processing of meaningful stimuli in cortical midline structures. These findings point to the crucial role of the 5-HT_{2A}R subtype and cortical midline regions in the generation and attribution of personal relevance. Our results thus increase our mechanistic understanding of personal relevance processing and reveal potential targets for the treatment of psychiatric illnesses characterized by alterations in personal relevance attribution.

Keywords: serotonin 2A receptor, lysergic acid diethylamide, personal relevance, meaning, music

Results

Subjective effects of LSD and role of $5HT_{2A}R$

Participants underwent three treatment conditions: placebo+placebo (Pla) condition: placebo after pretreatment with placebo; 2) placebo + LSD (LSD) condition: LSD after pretreatment with placebo; or 3) ketanserin+LSD (Ket+LSD) condition: LSD after pretreatment with the 5-HT_{2A} and α-adreno antagonist ketanserin. A repeated-measures (treatment × scale) analyses of variance (ANOVA) was conducted for the retrospectively administered Altered States of Consciousness (5D-ASC) questionnaire [4], and revealed significant main effects for treatment. ($F(1.00, 21.08) = 65.39$, $p < 0.001$) and scale (11 5D-ASC scales) ($F(4.99, 104.72) = 13.64$, $p < 0.001$), and a significant interaction of treatment × scale ($F(4.79, 100.57) = 12.24$, $p < 0.001$). Bonferroni-corrected simple main effect analyses revealed greater scores on nine of the 11 5D-ASC scales in the LSD treatment condition than in the Pla and Ket+LSD treatment conditions (all $p < 0.05$). Scores on the spiritual experience and anxiety scales did not differ across conditions (all $p > 0.30$). Scores did not differ between the Pla and Ket+LSD treatment conditions for any 5D-ASC scale (all $p > 0.90$) **(Figure 1)**.

To investigate treatment effects on mood state, a repeated-measures (time × treatment × scale) ANOVA was conducted for the Positive and Negative Affect Schedule (PANAS) [5] and revealed a significant main effect for scale ($F(1, 21) = 193.71$, $p < 0.001$), indicating a higher score on the positive affect scale than on the negative affect scale, a significant main effect for treatment ($F(1.52, 32.01) = 6.13$, $p < 0.01$), and significant interactions for treatment × time ($F(2, 42) = 19.01$, $p < 0.001$), time × scale ($F(1, 21) = 9.29$, $p < 0.01$), and treatment × time × scale ($F(2, 42) = 3.98$, $p < 0.05$). Bonferroni-corrected simple main effect analyses revealed that scores on the positive and negative affect scales did not differ between treatments before drug administration (all $p > 0.9$). After drug administration, score on the positive affect

scale was significantly greater in the LSD treatment condition than in both the Pla and Ket+LSD treatment conditions (all $p < 0.05$), and score on the negative affect scale was greater in the LSD treatment condition than in the Pla treatment condition ($p < 0.05$). Scores did not differ between the Pla and Ket+LSD treatment conditions for either the positive or negative affect scale (all $p > 0.9$) (**Fig. S1**).

In summary, LSD induced subjective effects as anticipated [6]. All of these LSD-induced effects were blocked by the 5-HT_{2A}R antagonist ketanserin, pointing to the key role of the 5-HT_{2A}R in mediating the human experience of LSD-induced effects.

Effects on LSD on the fabric of meaning

A core aspect of the concept of the self is the attribution of personal relevance to everyday stimuli [1]. Personal relevance has been described as the appraisal of external and internal stimuli with regard to their meaning for the organism [7]. Abnormalities in the attribution of personal relevance to stimuli are not only characteristic features of psychotic disorders including schizophrenia, but are also critical aspects of addiction, phobia, and mood disorders [2, 3]. It has been hypothesized that these alterations in personal relevance attribution may be related to changes in self-related processing, and that this may represent a pathophysiological mechanism underlying the deficits in self-awareness in various psychiatric disorders [2, 8]. Music is a powerful stimulus to elicit self-related processing [9]. Therefore, we investigated the neuropharmacology of personal relevance processing by testing the influence of LSD with and without ketanserin pretreatment on the processing of music otherwise experienced as personally meaningful, neutral, and personally not meaningful music (i.e., without personal meaning or relevance).

Pre-Task Questionnaire (PTQ): Outcomes of questions 1-3 (subjective experience of musical excerpts) are presented in **Table S1**. The mean rating for general personal meaningfulness of music was 7.00 [SD: 1.11; range 1 (not at all) – 9 (very)].

Ratings: A repeated-measures ANOVA (treatment × music condition) of meaningfulness ratings provided during the music paradigm revealed a significant main effect for treatment condition ($F(2,42) = 12.35$, $p < 0.001$) and music condition ($F(2,42) = 179.39$, $p < 0.001$). Bonferroni-corrected pairwise comparisons revealed that music was rated significantly more meaningful in the LSD treatment condition than in the Pla and Ket+LSD treatment conditions (all $p < 0.005$). Furthermore, as intended, meaningfulness ratings significantly differed across music conditions (all $p < 0.001$), with songs being rated highest in the meaningful condition and lowest in the meaningless condition. There was a significant treatment × music condition interaction ($F(2.28,47.78)=5.26$, $p < 0.01$). Simple main effects analysis revealed that meaningfulness ratings were increased in the meaningless and neutral music conditions in the LSD treatment condition compared to the Pla and Ket+LSD treatment conditions (all $p < 0.05$) (**Figure 2**).

Functional magnetic resonance imaging (fMRI): For results in the Pla condition see **Table S2** and **Figure S2**. The interaction of treatment condition x music condition revealed significant clusters in the left supplemental motor area (SMA) (peak: x=-7, y=1, z=66, k=5362, T=6.74), superior temporal gyrus (peak: x=51, y=15, z=-3, k=215, T=4.43), right posterior lobe of the cerebellum (peak: x=-27, y=-62, z-25, k=334, T=5.02), left hippocampus (peak: x=-18, y=-27, z=-12, k=102, T=4.07), inferior parietal lobule (peak: x=-53, y=-46, z=-35, k=460, T=4.31), and middle frontal gyrus (peak: x=49, y=-5, z=46, k=227, T=4.59).

Comparison of the "meaningless > meaningful" contrast between LSD and Pla treatment conditions revealed significantly greater blood-oxygenation-level dependent BOLD signal in

the left SMA after LSD administration (**Figure 3a** and **Table S2**). Furthermore, comparison of the "meaningless > neutral" contrast revealed greater BOLD signal in the bilateral vlPFC and left dorsomedial prefrontal cortex (dmPFC) after LSD treatment (**Figure 3b** and **Table S2**). No significant clusters were found for the other contrasts for the comparison of LSD and Pla treatment conditions. A direct comparison between listening to meaningful music after placebo administration and listening to meaningless music after LSD administration using a flexible factorial design did not result in any significant differences between these conditions.

Comparison of the "meaningless > meaningful" contrast between LSD and Ket+LSD treatment conditions revealed significantly greater BOLD signal in the left dorsal anterior cingulate cortex (dACC) after LSD administration that was not preceded by ketanserin (**Figure 4a** and **Table S2**). Furthermore, comparison of the "meaningless > neutral" contrast revealed significantly greater BOLD signal in the left dACC, left middle frontal gyrus, and left superior frontal gyrus after LSD administration that was not preceded by ketanserin (**Figure 4b** and **Table S2**). No significant clusters were found for the other contrasts.

Comparison of the "meaningful > meaningless" contrast between Pla and Ket+LSD treatment conditions revealed significantly greater BOLD signal in the right PCC after Ket+LSD administration (**Figure S3** and **Table S2**). No significant clusters were found for the other contrasts.

Parametric modulation was calculated to investigate the neural correlates of meaning processing by taking into consideration the meaningfulness ratings participants provided for each song trial. For results see **Figure S4** and **Table S3**.

In summary, listening to meaningless music (vs. neutral and personally meaningful music) in the LSD condition was associated with greater BOLD signal in lateral frontal brain areas and cortical midline structures including the SMA, dorsal anterior cingulate cortex and the dmPFC

compared to Pla and Ket+LSD treatment conditions. However, the BOLD signal in the posterior cingulate cortex was greater when listening to personally meaningful compared to personally meaningless music in the Ket+LSD treatment condition than in the Pla condition.

Discussion

The present study combined pharmacological manipulation with behavioral and neuroimaging methods to investigate the role of the 5-HT_{2A}R system in the generation and modulation of LSD's overall subjective psychedelic effects, and particularly altered personal relevance attribution, and the involved brain structures. LSD has high affinity and agonist activity at 5-$HT_{2A/C}$, 5-$HT_{1A/B}$, 5-HT_6, and 5-HT_7, and dopamine D2, D1 Rs [10-13]. However, no previous study had investigated the specific receptor contributions to the effects of LSD in humans. Our results show that subjective LSD-induced effects were fully blocked by a 5-HT_{2A}R antagonist. This is in line with animal studies that have highlighted the importance of the 5-HT_2 R system in the mechanism of action of LSD by showing that 5-HT_2 R antagonists blocked LSD-induced abnormal behavior in rodent models of psychiatric disorders [14, 15]. Furthermore, ketanserin also reduced psychedelic effects of the structurally related 5-$HT_{2A/1A}$R agonists psilocybin and ayahuasca [16, 17]. The present results demonstrate for the first time that in particular 5-HT_{2A}R activation is the key mechanism of action in mediating the unique human experience of psychedelic effects induced by the prototypical hallucinogen LSD.

The current result that all subjective effects of LSD on the 5D-ASC and PANAS questionnaires were blocked by ketanserin is somewhat surprising considering the high affinity of LSD to dopamine D2/D1 Rs [11, 18] and the apparent dopaminergic component of LSD-induced behavioral effects in a delayed temporal phase in rats [19]. Furthermore, the 5-HT_{1A}R has also been implicated in LSD-induced effects in animals and is supposed to excerpt opposite effects on 5-HT_{2A}R mediated behavior [20-25]. In humans, 5-HT_{1A} agonists such as buspirone reduced psilocybin-induced visual disturbances without affecting its effect on emotion [26], while 5-HT_{1A} antagonists increased the psychedelic effects of DMT [27]. While the current results indicate that the overall psychedelic effects of LSD including its effects on

mood are primarily mediated via 5-HT_{2A}R stimulation in humans, further studies blocking the D2/D1 Rs and 5-HT_{1A} Rs are necessary to clarify the specific role of these Rs in LSD-induced effects.

These results on subjective LSD-induced effects are consistent with behavioral ratings obtained in the music paradigm in the present study. Firstly, the rating of meaningfulness provided during the music paradigm significantly differed for the personally meaningful, neutral, and personally meaningless music excerpts with meaningful songs scoring highest and meaningless songs scoring lowest. This indicates that the selection and matching of music resulted in the intended experience of meaningfulness. Secondly, LSD significantly increased meaningfulness ratings for the previously meaningless and neutral music excerpts, an effect that was normalized by pretreatment with ketanserin. These results are in line with previous studies reporting an enhanced emotional response to music after LSD treatment [28, 29]. Importantly, the current results indicate that stimulation of the 5-HT_{2A}R alters the attribution of meaning to stimuli, and in particular leads to a higher attribution of meaning to otherwise meaningless cues. Therefore, the 5-HT_{2A}R may also be involved in dysfunctional personal relevance attribution observed in psychiatric disorders such as schizophrenia and addiction [2, 3, 30, 31]. Overattribution of personal relevance and potential consequences thereof should also be taken into account when LSD is considered to be used therapeutically.

In agreement with the behavioral ratings and with previous studies [9, 32], listening to personally meaningful music in the Pla treatment condition was associated with greater BOLD signal in the SMA, putamen, middle occipital gyrus, vlPFC, and cerebellum than listening to neutral and personally meaningless music. Furthermore, comparing the neutral and meaningless music conditions revealed significant clusters of activity in the dmPFC, dorsolateral prefrontal cortex, insula, precentral gyrus, superior and middle temporal gyrus, and angular gyrus. Activity in these brain areas has been associated with listening to

autobiographically salient and chill-inducing music [9, 32], the ascription of subjective value [33], the appraisal of external stimuli [34], and the processing of self-relevant stimuli [35]. Furthermore, these regions highly overlap with brain regions identified by a parametric modulation of their response taking into consideration the extent to which participants rated the music excerpts as meaningful. This indicates that predefined music categories and the according brain response reflect the attribution of personal meaning to music excerpts.

Importantly, when listening to meaningless music LSD significantly increased activation of the SMA compared to meaningful music and of the vlPFC and dmPFC compared to neutral music. Cortical midline regions including the SMA and the dmPFC as well as the lateral PFC are involved in self-referential cognition and self-relevant processing [35, 36]. Applying a meta-analytic approach, it has been suggested that the cortical midline regions are characterized by supramodal processing of self-related stimuli crucial for the transformation of simple sensory processing to more complex self-referential processing [36]. Furthermore, the authors of this meta-analysis linked the cortical midline structures to the concepts of “core”, “mental”, and “minimal” self, and linked the lateral PFC to higher order self-referential processing including autobiographical, emotional, and spatial aspects of the self [36]. The vlPFC has been associated with aberrant self-reflectiveness in schizophrenia patients [37]. The current results showed increased activity in these cortical midline regions and the vlPFC in response to "meaningless" stimuli in the LSD treatment condition, and are in accordance with the behavioral ratings suggesting that LSD increases the attribution of meaning to previously not meaningful stimuli. Furthermore, the results provide evidence that this alteration in relevance attribution is related to increased activity of brain areas that are typically involved in self-referential processing and are of clinical importance in psychiatric disorders characterized by altered self-processing [2, 8].

Analogous to the behavioral rating data, ketanserin blocked the LSD-induced increase in activation of self-related brain regions in response to previously non-meaningful stimuli. Firstly, there were no significant differences between Ket+LSD and Pla treatment conditions when comparing meaningless music excerpts to neutral or meaningful music excerpts. Secondly, activation of cortical midline and frontal structures for meaningless stimuli was greater in the LSD treatment condition than in the Ket+LSD treatment condition; namely in the dACC for the "meaningless > meaningful" contrast and the dACC, middle frontal gyrus, and superior frontal gyrus for the "meaningless > neutral contrast". Importantly, these regions also have a high 5-HT_{2A}R density [38]. Furthermore, there were no significant differences in BOLD signal between drug treatment conditions when taking into account the meaningfulness rating provided by the participants after each trial, indicating that brain activity reflected differences in meaning processing as behaviorally reported by the participants. In sum, these results corroborate our conclusion that stimulation of the 5-HT_{2A}R is key in the attribution of self-relevance and meaning to external stimuli.

The increase in BOLD signal in the PCC for the "meaningful > meaningless" contrast was greater in the Ket+LSD treatment condition than in the Pla treatment condition. The PCC has been associated with autobiographical memory retrieval [39] and experiential self-reflection [40]. Therefore, these results indicate increased processing of, and probably attribution of self-relevance to, external meaningful stimuli after Ket+LSD administration. Given that LSD has high affinity and agonistic activity at both 5-HT_{2A} and D2 Rs [10, 11] and that the 5-HT_{2A}R system was blocked by ketanserin in the Ket+LSD treatment condition, it is conceivable that the modulation of the processing of meaningful stimuli is attributable to dopaminergic R stimulation. This interpretation is in line with previous studies reporting a relation between PCC volume and dopamine levels in healthy humans [41], as well as studies linking dopaminergic dysfunction, e.g. increased firing of dopaminergic neurons, to altered salience

attribution in patients with schizophrenia [30, 42]. This increased attribution of meaning to self-relevant stimuli was not reflected in the meaningfulness ratings, which were not significantly different between Ket+LSD and Pla treatment conditions. However, meaningfulness ratings were close to the upper end of the scale in the Pla treatment condition (mean: 3.33; scale maximum: 4); therefore, a ceiling effect might have masked differences between conditions. This result has to be interpreted with the limitation in mind that the attribution to dopaminergic effects remains speculative, and other receptors stimulated by LSD could be involved. Furthermore, due to the design of the study the effects of LSD and ketanserin could not be investigated independently. A full factorial design is desirable in future studies. Moreover, further studies should be conducted to determine the role of various factors potentially contributing to altered meaning processing such as preference, depth of processing, or level of association.

In contrast to a previous study administering 200µg of LSD [6] we did not find significant increases of spiritual experiences in the LSD condition. We assessed spirituality with the spirituality scale of the Affective Neuroscience Personality Scales [43] at screening visit. This resulted in an average score of 14.09 (SD: 9.08) and is therefore lower than in previously published normative data assessing young adults [43]. Moreover, the rather clinical atmosphere in the MR environment may not have promoted spiritual experiences. Therefore, a combination of dose, personality, and setting variables may be responsible for this result.

In summary, by combining pharmacological stimulation, blocking of specific receptors, and behavioral and neuroimaging techniques, the current results illuminate the neural and neurochemical foundations of the attribution of meaning to the environment in humans. The results show, for the first time, that subjective LSD effects can be fully blocked by a 5-HT_{2A}R antagonist, highlighting the key role of the 5-HT_{2A}R subtype of 5-HT Rs in the mediation of the psychedelic effects of LSD in humans. Furthermore, the results suggest that LSD increases

the attribution of personal relevance to previously non-meaningful stimuli and that this effect is attributable to 5-HT_{2A}R stimulation and associated with activity in brain areas related to self-relevant processing. Additionally, treatment with Ket+LSD seems to modulate the processing of personally relevant stimuli, possibly due to LSD-induced dopamine R stimulation. The current results therefore emphasize the importance of the 5-HT_{2A}R subtype in the generation of personal meaning and point to the involvement of the dopamine system in the further modulation of personal relevance. Abnormalities in the attribution of personal relevance to stimuli are clinically relevant features of various psychiatric disorders [2, 3, 31]. The current findings therefore increase our mechanistic understanding of the neurochemical underpinnings of personal meaning processing and attribution, and reveal prospective differential targets for the treatment of psychiatric illnesses characterized by alterations in personal relevance attribution.

Experimental Procedures

Participants

For details see **Supplemental Experimental Procedures** and **Table S4**.

Study Design

In a double-blind, randomized, cross-over design, participants received either: 1) placebo+placebo (Pla) condition: placebo (179 mg Mannitol and 1 mg Aerosil po) after pretreatment with placebo (179 mg Mannitol and 1 mg Aerosil po);, 2) placebo + LSD (LSD) condition: LSD (100 µg po) after pretreatment with placebo (179 mg Mannitol and 1 mg Aerosil po); or 3) ketanserin+LSD (Ket+LSD) condition: LSD (100 µg po) after pretreatment with the 5-HT2A and α-adreno antagonist ketanserin (40 mg po). For details and assessment of subjective effects see **Supplemental Experimental Procedures.**

Music Paradigm

On the screening visit, participants provided six songs that were of particular personal relevance to them and indicated the most meaningful 20 s of each song. Personally meaningless and neutral music experts were matched to these songs (see **Supplemental Experimental Procedures**). For MR Data acquisition and Preprocessing and Statistical Analysis see **Supplemental Experimental Procedures.**

Author contributions

K.H.P., M.H., M.E.L., and F.X.F. designed the research. K.H.P., T.P., A.P., R.K., and P.S. carried out the experiment. K.H.P. and A.P. analyzed the data. K.H.P., M.H., E.S., and F.X.V. wrote the manuscript. All authors approved the manuscript.

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Figure Legends

Figure 1. Subjective drug effects. See also Figure S1. Retrospectively assessed 5D-ASC scores in the Placebo (Pla), Ketanserin+LSD (Ket+LSD), and LSD treatment conditions. Scores are expressed as a percent of the scale maximum (n = 22 participants). Scores in the LSD treatment condition differed significantly from Placebo and Ketanserin+LSD treatment conditions on each scale except for spiritual experience and anxiety ($p < 0.05$, Bonferroni corrected).

Figure 2. Meaningfulness ratings for personally meaningful, neutral, and personally meaningless songs in the Placebo (Pla), Ketanserin+LSD (Ket+LSD), and LSD treatment conditions. Meaningfulness ratings for the meaningless and neutral songs were greater in the LSD treatment condition than in the Pla and Ket+LSD treatment conditions. Data are expressed as mean ± standard error of the mean. Asterisks indicate significant differences between LSD and Pla treatment conditions and LSD and Ket+LSD treatment conditions (*$p < 0.05$, n = 22).

Figure 3. fMRI data in the LSD > Placebo comparison. See also Figure S2, Figure S3 and Table S2 A) "meaningless > meaningful" contrast at peak SMA voxel (x = -15, y = -16, z = 63); B) "meaningless > neutral" contrast at peak dmPFC voxel (x = 2, y = 34, z = 38). Data displayed at $p < 0.001$ (uncorrected), n = 22.

Figure 4. fMRI data in the LSD > Ketanserin+LSD comparison. See also Table S2. A) "meaningless > meaningful" contrast at peak dACC voxel (x = -7, y = 23, z = 30); B) "meaningless > neutral" contrast at peak dACC voxel (x = -1, y = -27, z = 24). Data displayed at $p < 0.001$ (uncorrected), n = 22.